Supplementary Material

Synthesis and docking studies of thiophene scaffolds in COX-2

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1. Supplementary data

In case of **4** and **7** (Figure S1c, Table S1), former interacts simultaneously with two amino acid residues His386 and Gln454 (His386NH…CO…NHGln454) whereas later exhibits two concurrent intermolecular H bonds (CO…NHHis386….OCH_3) with His386. Moreover, His214 and His 207 form cation-π linkages with the thiophene and aromatic rings of the compound 4, respectively. Compound **6** form bifurcated intermolecular H bonds with His386 (CO…HNHis386…S) while **9** interacts with His386 through single H bond (Figure S1d, Table S1). Where compound **6** show two cation-π interactions by aligning its aromatic and thiophene rings perpendicular to the imidazole rings of the His207 and His214, the compound **9** interacts strongly (3.2Å) through its thiophene π- electorns with the imidazole ring of His386. Compound **8,** in addition to two cation-π interactions with His207 and His214 through its tolyl and thiophene rings, also form bifurcated intermolecular H bonds (CO…HNHis386…S) with His386, whereas **10** interact only through single H bond with His386 (Figure S2a, Table S1). Compounds **11** and **12**, in addition to cation-π interactions similar to that of **6** and **8** interact through single H bond with Gln454 and His386, respectively as shown in Figure S2b. The compounds **9** and **14** bearing 1,3-thiazine and thiopyran rings in their structures, in contrast to thiophene compounds **6a-6l**, failed to show any interactions with the binding site of COX-2.

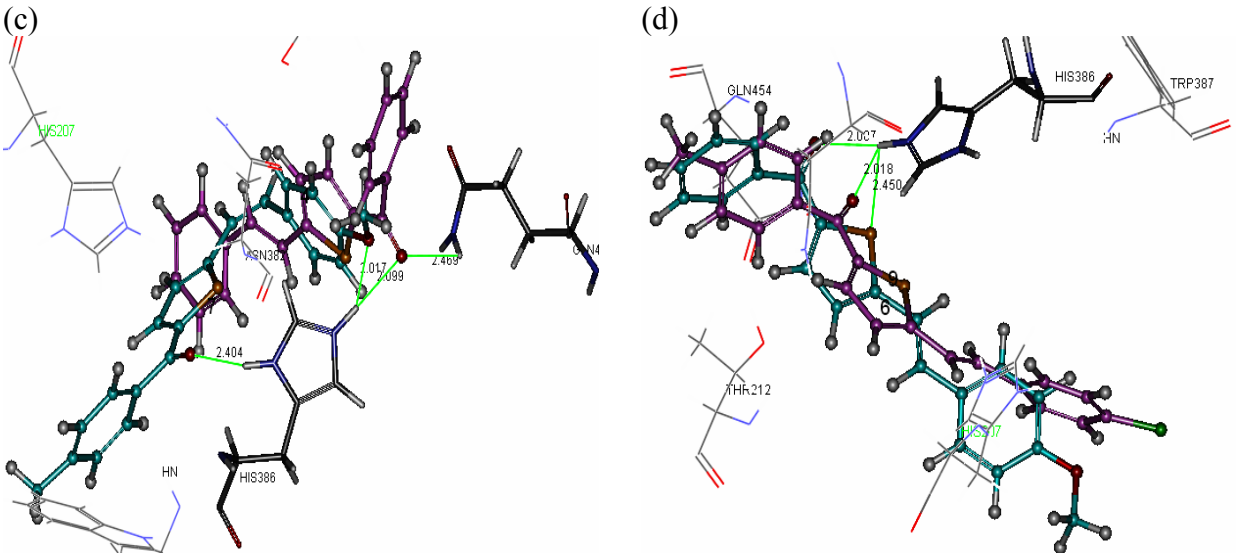


Figure S1. Docked conformations of compounds **4,7** (c) and **6,9** (d) showing important amino acid residues of COX-2. Ligands are shown as ball and stick, and the interacting amino acids are shown as sticks. H Bonds shown in green.

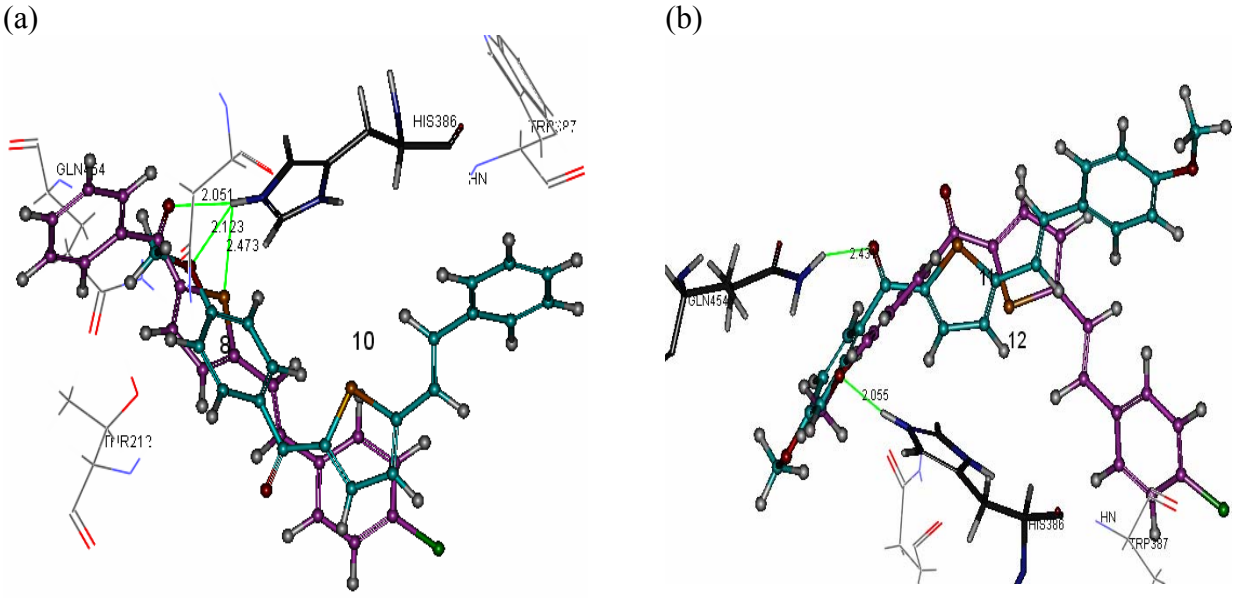
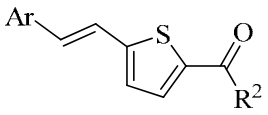


Figure S2. Docked conformations of compounds **8,10** (a) and **11,12** (b) showing important amino acid residues of COX-2. Ligands are shown as ball and stick, and the interacting amino acids are shown as sticks. H Bonds shown in green.

Table S1. Docking results of thiophene derivatives **6a-6l** with COX-2



Candidate Code	Compounds	Ar	R^2	No. of H-bonds	Donor/Acceptor Hydrogen bond	H-bond distance (Å)	Binding energy (kcal/mol)
1	6a	Phenyl	$-OCH_2CH_3$	1	CO……NH (TRP 387)	2.17	-6.30
2	6e	4-methoxyphenyl	$-OCH_2CH_3$	1	S……NH(HIS 386)	2.49	-6.32
3	6i	4-chlorophenyl	$-OCH_2CH_3$	1	CO……..NH (HIS 386)	2.04	-6.29
4	6b	Phenyl	Phenyl	2	CO……NH (HIS 386)	2.09	-6.31
					CO……...NH (GLN454)	2.46	-
5	6d	Phenyl	4-methylphenyl	1	CO…….NH (HIS 386)	1.86	-6.26
6	6f	4-methoxyphenyl	Phenyl	2	CO…….NH (HIS 386)	2.08	-6.27
					S……NH (HIS386)	2.45	-
7	6h	4-methoxyphenyl	4-methylphenyl	2	CO…….NH (HIS 386)	2.40	-6.25
					CH_3O……..NH (HIS386)	2.02	
8	6j	4-chlorophenyl	Phenyl	2	CO…….NH (HIS 386)	2.05	-6.30
					S……NH (HIS386)	2.47	-
9	6l	4-chlorophenyl	4-methylphenyl	1	CO…….NH (HIS 386)	2.02	-6.26

Table S1. Continued

Candidate Code	Compounds	Ar	R^2	No. of H-bonds	Donor/Acceptor Hydrogen bond	H-bond distance (Å)	Binding energy (kcal/mol)
10	6c	Phenyl	4-methoxyphenyl	1	CO…….NH (HIS 386)	2.12	-6.23
11	6g	4-methoxyphenyl	4-methoxyphenyl	1	CO…….NH (GLN 454)	2.43	-6.27
12	6k	4-chlorophenyl	4-methoxyphenyl	1	CH_3O……..NH (HIS386)	2.05	-6.24
					CO…….NH (HIS 207)	1.98	-

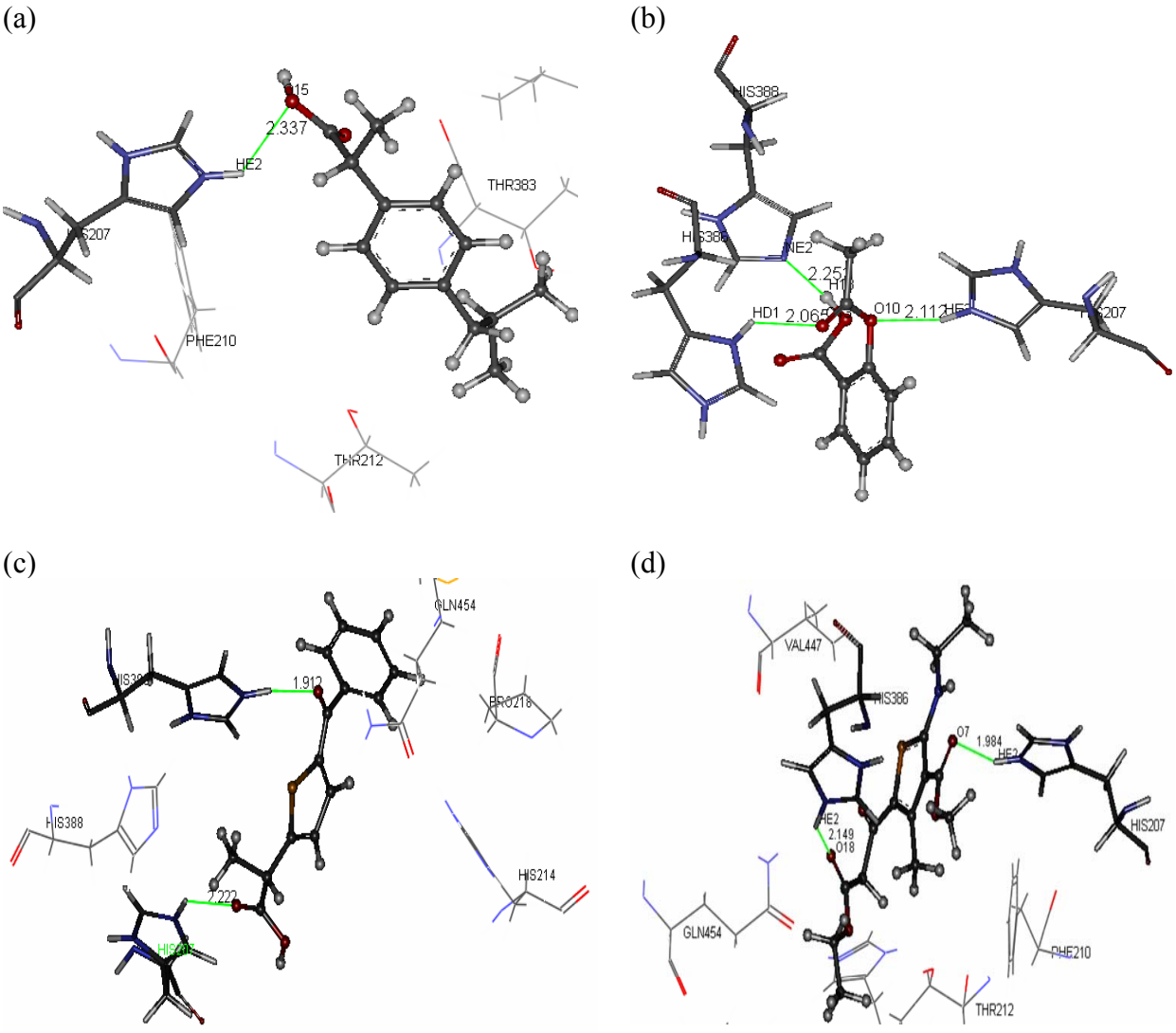


Figure S3. Docked conformations of Ibuprofen (a), Aspirin (b), TA (c) and compound e (d) showing important amino acid residues of COX-2. Ligands are shown as ball and stick, and the interacting amino acids are shown as sticks. H Bonds shown in green.

Table S2. Docking results of NSAIDs and compound e with COX-2

Compound	Number of H-bonds	Donor/Acceptor Hydrogen bond	H-bond distance (Å)	Binding energy (kcal/mol)
Ibuprofen	1	COO……NH(His 207)	2.337	-6.10
Aspirin	3	COOH……..N(His388)	2.252	-6.16
		CH_3CO….HN(His386)	2.065	-
		CH_3COO….HN(His207)	2.112	-
TA	2	CO…….NH(HIS 386)	1.91	-6.19
		CO…….NH(HIS 207)	2.22	-
Compound f	2	CO…….NH(HIS 386)	2.14	-6.25
		CO…….NH(HIS 207)	1.98	-